

# Clinical Correlations With Dermatomyositis-Specific Autoantibodies in Adult Japanese Patients With Dermatomyositis

## A Multicenter Cross-sectional Study

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**Objective:** To clarify the association of clinical and prognostic features with dermatomyositis (DM)-specific autoantibodies (Abs) in adult Japanese patients with DM.

**Design:** Retrospective study.

**Setting:** Kanazawa University Graduate School of Medical Science Department of Dermatology and collaborating medical centers.

**Patients:** A total of 376 consecutive adult Japanese patients with DM who visited our hospital or collaborating medical centers between 2003 and 2008.

**Main Outcome Measures:** Clinical and laboratory characteristics of adult Japanese patients with DM and DM-specific Abs that include Abs against Mi-2, 155/140, and CADM-140.

**Results:** In patients with DM, anti-Mi-2, anti-155/140, and anti-CADM-140 were detected in 9 (2%), 25 (7%), and 43 (11%), respectively. These DM-specific Abs were mutually exclusive and were detected in none of 34 patients with polymyositis, 326 with systemic sclerosis, and 97 with systemic lupus erythematosus. Anti-Mi-2 was associated with classical DM without interstitial lung disease or malignancy, whereas anti-155/140 was associated with malignancy. Patients with anti-CADM-140 frequently had clinically amyopathic DM and rapidly progressive interstitial lung disease. Cumulative survival rates were more favorable in patients with anti-Mi-2 compared with those with anti-155/140 or anti-CADM-140 ( $P < .01$  for both comparisons). Nearly all deaths occurred within 1 year after diagnosis in patients with anti-CADM-140.

**Conclusion:** Dermatomyositis-specific Abs define clinically distinct subsets and are useful for predicting clinical outcomes in patients with DM.

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**P**OLYMYOSITIS (PM) AND DERMATOMYOSITIS (DM) represent a group of chronic inflammatory disorders characterized by myogenic changes, skin eruptions, or both. Clinical features are heterogeneous, with various degrees of skin manifestations, myositis, and pulmonary involvement, which

*For editorial comment  
see page 492*

considerably determine the severity and prognosis.<sup>1</sup> Although the causes of these disorders remain unclear, autoimmunity is considered to have a critical role because the presence of diagnostic autoantibodies (Abs),

known as myositis-related Abs, is a prominent feature.<sup>2</sup> A variety of serum Abs are detected in patients with PM/DM, including Abs reactive with aminoacyltransfer RNA synthetase (ARS),<sup>3</sup> signal recognition particle,<sup>4</sup> and Mi-2.<sup>5</sup> These Abs are associated with clinically distinct subsets of PM/DM, that is, anti-ARS with interstitial lung disease (ILD), arthritis, Raynaud phenomenon, and mechanic hand<sup>6,7</sup>; anti-signal recognition particle with acute-onset severe refractory PM<sup>8-10</sup>; and anti-Mi-2 with typical DM with a lower risk of ILD and internal malignancy and good response to treatment.<sup>11-13</sup> In addition, anti-PM-Scl, anti-Ku, and anti-U1RNP Abs are associated with myositis overlap syndrome.<sup>14</sup> Therefore, identification of myositis-related Abs is use-

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ful in defining clinically homogenous patient subsets, in predicting prognosis, and in clarifying the pathogenesis. Recently, 2 myositis-related Abs, anti-155/140<sup>15,16</sup> and anti-CADM-140,<sup>17</sup> have been reported. Subsequent studies have revealed corresponding autoantigens: transcriptional intermediary factor 1- $\gamma$  for anti-155/140<sup>18</sup> and melanoma differentiation-associated gene 5 for anti-CADM-140.<sup>19</sup> Anti-155/140 Abs are reported to represent malignancy-associated or juvenile DM,<sup>15,20</sup> and anti-CADM-140 Abs are reported to be associated with amyopathic DM and rapidly progressive ILD (RP-ILD).<sup>17,19</sup> Although precise clinical details of these 2 Abs need to be clarified further, anti-155/140, anti-CADM-140, and anti-Mi-2 Abs are considered to be highly specific for DM.

To our knowledge, this is the first large comprehensive study that includes all currently available myositis-related Abs intended for a variety of adult Japanese patients with DM. We focused particularly on anti-Mi-2, anti-155/140, and anti-CADM-140 and attempted to investigate a correlation between these 3 DM-specific Abs and clinical features and prognosis in detail.

## METHODS

### PATIENTS AND SERUM SAMPLES

Serum samples were obtained from 376 adult Japanese patients with DM who were observed in the Department of Dermatology, Kanazawa University, Kanazawa, Japan, and collaborating medical centers between January 1, 2003, and December 31, 2008. Of the 376 patients with DM, 325 fulfilled the criteria of Bohan and Peter.<sup>21,22</sup> The remaining 51 patients fulfilled the criteria of Sontheimer<sup>23</sup> because of the absence of clinical muscle symptoms and the presence of subsistent clinical DM skin eruptions. Clinically amyopathic DM included patients with amyopathic DM and patients with hypomyopathic DM. Patients with hypomyopathic DM had DM rash and subclinical evidence of myositis on electrophysiologic, radiologic, or laboratory evaluation.<sup>24</sup> Thirteen patients (5 with anti-155/140 Abs and 8 with anti-CADM-140 Abs) who were observed at Nagasaki University<sup>25</sup> were included in this study. As controls, serum samples from 34 patients with PM, 326 with systemic sclerosis, and 97 with systemic lupus erythematosus who were observed during the same period were also assessed. The diagnosis of PM was based on the criteria of Bohan and Peter.<sup>21,22</sup> All the patients with systemic lupus erythematosus or systemic sclerosis fulfilled the American Rheumatism Association criteria.<sup>26,27</sup> A PM/DM overlap was diagnosed by the coexistence of systemic lupus erythematosus or systemic sclerosis in addition to PM or DM.

Clinical information was collected retrospectively from all the patients by reviewing their clinical medical records. Initial symptoms were defined as clinical presentation at the first clinic visit. Muscle involvement in an initial symptom included clinical signs of muscle disease or abnormality evaluated using electrophysiologic, radiologic, or laboratory tests. The patients were diagnosed as having ILD according to the results of chest radiography, chest computed tomography, and pulmonary function tests, which included the percentage predicted values for forced vital capacity and diffusing capacity for carbon monoxide. A subset of patients with RP-ILD was defined as those with progressive dyspnea and progressive hypoxemia and a worsening of interstitial changes on the chest radiograph within 1 month from the onset of respiratory symptoms. Malignancy that included internal and hematologic malignancy in patients with

DM was defined using criteria described previously.<sup>11</sup> No patient with DM had a history of malignant disease. The protocol was approved by the Kanazawa University Graduate School of Medical Science and Kanazawa University Hospital.

## IMMUNOPRECIPITATION

Immunoprecipitation (IP) assays were performed using extracts of the leukemia cell line K562.<sup>17</sup> A total of 10  $\mu$ L of the patient's serum was bound to 2 mg of protein A-Sepharose beads (Amersham Biosciences, Piscataway, New Jersey) in 500  $\mu$ L of IP buffer (10mM Tris hydrochloride, pH 8.0; 50mM sodium chloride; and 0.1% Nonidet P-40 [Caledon Laboratories Ltd, Georgetown, Ontario, Canada]) and was incubated for 2 hours at 4°C and then washed 5 times with IP buffer. Autoantibody-coated Sepharose beads were mixed with 100  $\mu$ L of <sup>35</sup>S-methionine-labeled K562 cell extracts derived from 10<sup>6</sup> cells and rotated at 4°C for 2 hours. After 5 washes, the beads were resuspended in sodium dodecyl sulfate sample buffer, and the polypeptides were fractionated by 7.5% sodium dodecyl sulfate-polyacrylamide gel electrophoresis followed by autoradiography. Anti-Mi-2 immunoprecipitated polypeptides of 200 to 240, 150, and 65 to 75 kDa, and anti-155/140 immunoprecipitated 155- and 140-kDa proteins. Anti-Mi-2, anti-155/140, and anti-CADM-140 were considered positive if serum samples produced precipitin lines with immunologic identity to reference sera.<sup>13,15,17</sup>

### IDENTIFICATION OF ANTI-CADM-140

The presence of anti-CADM-140 was confirmed in serum samples that immunoprecipitated a protein with a molecular weight of 140 kDa by IP assay by immunoblots and enzyme-linked immunosorbent assay using recombinant melanoma differentiation-associated gene 5 as an antigen.<sup>19</sup> This procedure aimed to exclude several other Abs, such as anti-NXP-2 (previously termed MJ),<sup>28</sup> that target a protein of approximately 140 kDa.

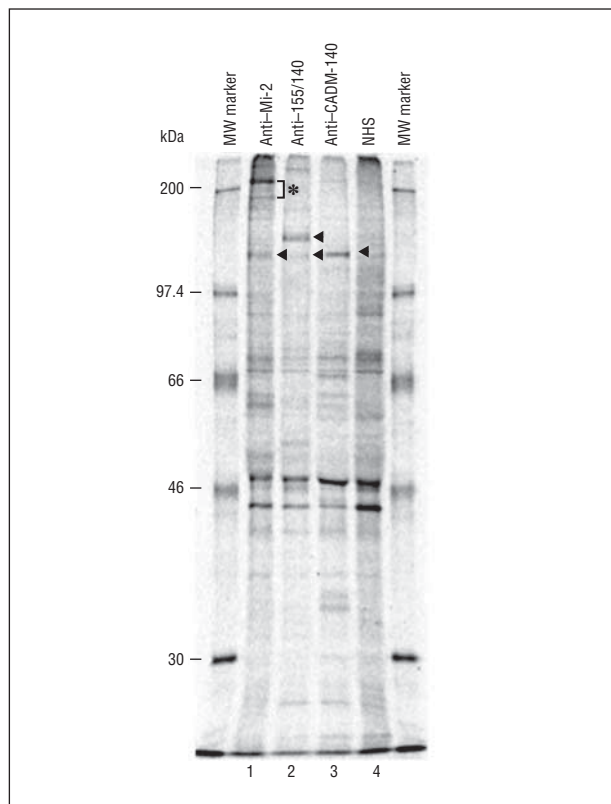
## STATISTICAL ANALYSIS

The Fisher exact probability test was used for comparison of frequencies, and 1-factor analysis of variance was used for multiple comparisons. *P* < .05 was considered statistically significant. All data are reported as mean (SD).

## RESULTS

### DISEASE SPECIFICITY OF THE MYOSITIS-RELATED Abs

**Figure 1** shows representative results of an IP assay. A total of 47 serum samples from patients with DM immunoprecipitated a protein with a molecular weight of approximately 140 kDa. Of these samples, 43 (91%) were reactive with melanoma differentiation-associated gene 5 by immunoblots and enzyme-linked immunosorbent assay, confirming the presence of anti-CADM-140. The frequencies of myositis-related Abs in patients with PM, DM, systemic sclerosis, and systemic lupus erythematosus are summarized in **Table 1**. Anti-Mi-2 antibodies were found in 2% of serum samples from patients with DM, anti-155/140 in 7%, and anti-CADM-140 in 11%, but none of these 3 DM-related Abs was detected in patients with PM or other connective tissue diseases. In addition, they did not coexist. These 3 Abs accounted for 21% of all patients with DM.



**Figure 1.** Immunoprecipitation assay of autoantibodies related to dermatomyositis. Immunoprecipitation of  $^{35}\text{S}$ -methionine-labeled K562 cell extracts was performed on serum samples from patients with dermatomyositis (lanes 1-3) and on normal human serum (NHS) (lane 4), separated on 7.5% sodium dodecyl sulfate–polyacrylamide gel electrophoresis, and analyzed by autoradiography. The molecular weight (MW) marker lane includes protein bands corresponding to 200, 97.4, 66, 46, and 30 kDa. Arrowheads indicate Mi-2 (lane 1), 155/140 (lane 2), and CADM-140 (lane 3) proteins. \*Two hundred–to 240-kDa proteins of Mi-2.

### COMPARISON OF CLINICAL FEATURES AMONG PATIENTS WITH DM WITH DM-SPECIFIC Abs

First, we compared the rates of malignancy and ILD in the 77 patients with the 3 DM-specific Abs and the 299 patients with DM who did not have any of the 3 DM-specific Abs (**Table 2**). Interstitial lung disease was seen most frequently in patients with anti-CADM-140 Abs, and the incidence of malignancy was highest in patients with anti-155/140 Abs ( $P < .001$  for all comparisons).

Next, we compared demographic, clinical, and laboratory data in each DM-specific Ab-based subgroup (**Table 3**). Patients with anti-CADM-140 had the lowest prevalence of DM but the highest prevalence of clinically amyopathic DM ( $P < .001$  and  $P < .001$ , respectively, for all comparisons). Regarding initial symptoms, although muscle or muscle and skin involvement is less common in clinically amyopathic DM, the addition of ILD led to a higher prevalence of combined muscle, skin, and lung disease in the anti-CADM-140 subset ( $P < .04$  for all comparisons). For clinical features, fever and arthritis were most frequently seen in patients with anti-CADM-140 ( $P < .001$  and  $P = .02$ , respectively, for all comparisons). Patients with anti-CADM-140 had ILD at the highest rates ( $P < .001$  for all comparisons), whereas ma-

**Table 1. Frequency of Myositis-Related Autoantibodies in Patients With Connective Tissue Diseases**

Autoantibodies	Patients, No. (%)				
	DM (n=376)	PM (n=34)	PM/DM Overlap (n=21)	SSc (n=326)	SLE (n=97)
Anti-Jo-1	21 (6)	4 (12)	0	1 (0.3)	0
Anti-ARS excluding anti-Jo-1	49 (13)	6 (18)	0	7 (2)	1 (1)
Anti-SRP	7 (2)	2 (6)	0	1 (0.3)	0
Anti-Mi-2	9 (2)	0	0	0	0
Anti-155/140	25 (7)	0	0	0	0
Anti-CADM-140	43 (11)	0	0	0	0
Anti-U1RNP	11 (3)	1 (3)	8 (38)	20 (6)	19 (20)
Anti-PM-Scl	0	0	0	0	0
Anti-Ku	2 (0.5)	3 (9)	6 (29)	3 (1)	0

Abbreviations: anti-ARS, anti-aminoacyltransfer RNA synthetase; anti-SRP, anti-signal recognition particle; DM, dermatomyositis; PM, polymyositis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

**Table 2. Malignancy and Interstitial Lung Disease in Patients With DM Without Autoantibodies to Mi-2, 155/140, or CADM-140 and Patients With DM With These 3 Autoantibodies<sup>a</sup>**

Variable	Patients, No. (%)			
	Anti-Mi-2 Positive (n=9)	Anti-155/140 Positive (n=25)	Anti-CADM-140 Positive (n=43)	Others (n=299)
Interstitial lung disease	1 (11)	3 (12)	40 (93)	105 (35)
Malignancy	0	17 (68)	4 (9)	18 (6)

Abbreviation: DM, dermatomyositis.

<sup>a</sup> $P < .001$  for all.

lignancy was most frequently seen in patients with anti-155/140 ( $P < .001$  for all comparisons). Malignancies were observed in 17 of 25 patients with anti-155/140 Abs, and 3 of those had double malignancy: 7 patients with lung cancer, 3 with breast cancer, 2 with colon cancer, 2 with gastric cancer, and a single case of prostate, biliary tract, pancreas, ovarian, and nasopharyngeal cancer and non-Hodgkin lymphoma. Ten of 17 patients with malignancy simultaneously developed DM, and 6 of 17 had malignancy before the development of DM.

Regarding skin eruptions, punctate hemorrhages on the perionychium were most frequently seen in patients with anti-Mi-2 ( $P = .04$  for all comparisons). In patients with anti-155/140, punctate hemorrhages on the perionychium were more frequently seen in those without malignancy than in those with malignancy ( $P = .007$ ) (**Table 4**). The frequency of truncal erythema in patients with anti-CADM-140 was lowest among the 3 subgroups ( $P = .001$  for all comparisons). On the other hand, patients with anti-CADM-140 had skin ulcers most frequently among the 3 subgroups ( $P < .008$  for all comparisons). However, the presence of skin ulcers was not a prognostic marker in patients with anti-CADM-140 (**Table 5**).

**Table 3. Demographic, Clinical, and Laboratory Features in 77 Japanese Patients With DM According to the Presence of 3 DM-Specific Autoantibodies**

Variable	Anti-Mi-2 Positive (n=9)	Anti-155/140 Positive (n=25)	Anti-CADM-140 Positive (n=43)	P Value
Age at onset, median (range), y	45 (16-66)	62 (31-79)	53 (15-76)	.005
Sex, M/F, No.	6/3	11/14	9/34	.01
Diagnosis, %				
Classical DM	100	72	23	<.001
Clinically amyopathic DM	0	28	77	<.001
Initial symptom, %				
Skin alone	44	40	35	.80
Muscle alone	11	4	0	.14
Lung alone	0	0	5	.44
Skin and muscle	44	44	12	.005
Skin and lung	0	4	21	.80
Muscle and lung	0	0	0	...
Skin, muscle, and lung	0	8	28	.04
Clinical features, %				
Fever	22	24	74	<.001
Raynaud phenomenon	0	12	28	.12
Muscle weakness	100	72	23	.02
Arthritis	11	8	42	.02
Interstitial lung disease	11	12	93	<.001
Malignancy	0	68	9	<.001
Skin eruptions, %				
Heliotrope rash	67	72	56	.37
Facial erythema other than heliotrope rash	56	88	51	.12
Gottron sign (hand)	89	96	86	.41
Gottron sign (elbow or knee)	56	76	77	.32
Periungual erythema	89	76	72	.67
Punctate hemorrhages on the perionychium	89	44	37	.04
Truncal erythema	89	88	35	<.001
Skin ulcers	0	4	30	.008
Cutaneous calcification	11	0	2	.29
Laboratory findings, mean (SD)				
CK, U/L	5283 (3649)	1364 (2263)	425 (1667)	<.001
LDH, U/L	814 (439)	564 (726)	547 (241)	.38
KL-6, U/mL	378 (1553)	476 (527)	2122 (1923)	<.001

Abbreviations: CK, creatine kinase; DM, dermatomyositis; ellipsis, not applicable; LDH, lactate dehydrogenase.  
SI conversion factors: To convert CK and LDH to microkats per liter, multiply by 0.0167.

**Table 4. Clinical and Laboratory Features in 25 Anti-155/140 Antibody-Positive Patients With Dermatomyositis by the Presence or Absence of Malignancy**

Variable	Malignancy Present (n=17)	Malignancy Absent (n=8)	P Value
Age at onset, median (range), y	68 (54-79)	49 (31-63)	<.001
Follow-up, mean, y	1.8	3.5	.06
Sex, M/F, No.	10/7	1/7	.04
Clinical features, %			
Muscle involvement <sup>a</sup>	71	100	.14
Arthritis	12	0	>.99
Interstitial lung disease	12	13	>.99
Skin eruptions, %			
Punctate hemorrhages on the perionychium	24	88	.007

<sup>a</sup>Muscle involvement included muscle weakness and subclinical myositis.

Regarding laboratory findings, maximum serum creatine kinase levels were significantly lower in patients with anti-CADM-140 than in those with anti-Mi-2 and anti-155/140 ( $P < .001$  for all comparisons). KL-6 is a mucin-like high-molecular weight glycoprotein that is strongly ex-

pressed on type II alveolar pneumocytes and bronchiolar epithelial cells. Serum KL-6 levels are associated with the activity and severity of ILD.<sup>29</sup> Serum KL-6 levels were higher in patients with anti-CADM-140 than in those with anti-Mi-2 and anti-155/140 ( $P < .001$  for all comparisons).



## TREATMENT AND PROGNOSIS IN PATIENTS WITH DM WITH DM-SPECIFIC Abs

The treatment regimens and prognosis of individual patients with anti-Mi-2, anti-155/140, and anti-CADM-140 are summarized in eTable 1, eTable 2, and eTable 3, respectively (available at <http://www.archdermatol.com>). Although most patients with anti-Mi-2 responded well to the initial therapy, 6 of 9 patients had a recurrence of muscle or skin involvement during follow-up. In 15 of 17 patients (88%) with anti-155/140 who had malignancy, treatment for malignancy did not improve the symptoms of DM. Effective initial and additional treatments in patients with anti-CADM-140 were not elucidated in this study (Table 5).

We assessed the survival rates between disease subsets (**Figure 2**). Overall cumulative survival from the time of DM diagnosis in all 77 patients with DM was 65% at 5 years. Survival in patients with anti-155/140 and those with anti-CADM-140 was 68% and 56% at 5 years, respectively. Both cumulative survival rates were significantly decreased compared with those for patients with anti-Mi-2 ( $P = .01$  for both). The cumulative rates were not identical between patients with anti-155/140 and those with anti-CADM-140 because RP-ILD in patients with anti-CADM-140 often developed rapidly in a short period after onset of the disease.

The prognosis of patients with anti-Mi-2 was favorable: no patients had malignancy and only 1 had mild ILD (Table 3). Although 8 patients (32%) with anti-155/140 died mainly from progression of malignancy during follow-up, the prognosis of anti-155/140-positive patients without malignancy was favorable. No significant trend was observed concerning the type of malignancy in anti-155/140-positive patients. Although patients with anti-CADM-140 whose prognosis was poor had significantly increased serum KL-6 levels ( $P = .04$ ), no apparent negative prognostic factors were noted in those with anti-CADM-140 who died (Table 5).

### CAUSE OF DEATH

Twenty-seven of 77 patients with DM died during follow-up. Of the 25 patients with anti-155/140, 7 died of malignancy and 1 died of bacterial pneumonia. Of the 43 anti-CADM-140-positive patients, 16 died of ILD and 1 died of *Pneumocystis jiroveci* pneumonia. One anti-CADM-140-positive patient died of disseminated intravascular coagulation. Thus, the major cause of death in patients with DM was associated with DM-related internal organ involvement. This is consistent with previous reports that malignancy and ILD are the major causes of death in patients with DM.

### COMMENT

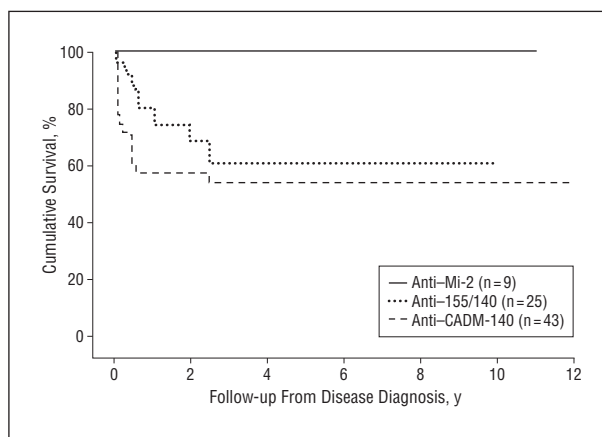
In this study, we compared clinical features and prognosis in adult Japanese patients with DM based on their DM-specific Abs. This study includes 3 major findings. First, to our knowledge, this is the first study to investigate the association of clinical features with 3 DM-

**Table 5. Clinical and Laboratory Features in 43 Anti-CADM-140 Autoantibody-Positive Patients With Dermatomyositis by Prognosis**

Variable	Dead (n=19)	Alive (n=24)	P Value
Age at onset, median (range), y	58 (30-76)	50 (15-74)	.06
Sex, M/F, No.	4/15	5/19	>.99
Clinical features, %			
Fever	74	75	>.99
Muscle involvement <sup>a</sup>	26	67	.01
Arthritis	32	50	.34
Interstitial lung disease	100	88	.24
Pneumomediastinum	32	13	.26
Type of ILD, %			
Rapidly progressive	89	54	.02
Classical	11	33	.14
Skin eruptions, %			
Heliotrope rash	42	63	.35
Facial erythema other than heliotrope rash	32	67	.06
Punctate hemorrhages on the perionychium	26	46	.19
Truncal erythema	16	46	.09
Skin ulcers	16	42	.10
Laboratory findings, mean (SD)			
KL-6, U/mL	2656 (1989)	1703 (1803)	.04
Initial treatment, %			
Prednisolone only	26	58	.06
Prednisolone and methylprednisolone pulse	63	29	.13
Additional treatment, %			
Methylprednisolone pulse	74	50	.06
Cyclophosphamide	53	42	.55
Cyclosporine	79	54	.12

Abbreviation: ILD, interstitial lung disease.

<sup>a</sup>Muscle involvement included muscle weakness and subclinical myositis.



**Figure 2.** Cumulative survival rates from the time of diagnosis in 77 Japanese patients with dermatomyositis with serum anti-Mi-2, anti-155/140, and anti-CADM-140 autoantibodies. Cumulative survival rates were compared using log-rank tests.

specific Abs in adult Japanese patients with DM on a large scale. Second, the 3 DM-specific Abs are mutually exclusive and do not coexist. Third, each of these DM-specific Abs defines a clinically distinct phenotype and may work as a predictor of clinical complications and

prognosis. Thus, classifying patients with DM based on their serum Ab profiles seems to be beneficial for focusing on their clinical features.

In an association of myositis-related Abs with the connective tissue diseases, PM/DM overlap was associated with anti-U1RNP and anti-Ku, and Abs detected in PM were predominantly anti-ARS and anti-signal recognition particle, as previously reported.<sup>4,30,31</sup> We also confirmed that anti-Mi-2, anti-155/140, and anti-CADM-140 were specific to DM in adult Japanese connective tissue diseases, and this finding was consistent with previous studies<sup>5,16,20,30</sup> assessing other ethnic groups.

Clinical characteristics of patients with anti-Mi-2 in this study were generally consistent with previous studies that anti-Mi-2 is associated with typical cutaneous lesions and mild to moderate muscle involvement and responds well to corticosteroid treatment.<sup>5,11-13</sup> However, recurrence of skin or muscle involvement might not be as rare as expected. Thus, although the overall prognosis is favorable, it is important to keep in mind that intractable myositis and rashes can occur, and careful observation is needed for monitoring flare-ups of the disease.

In this study, malignancy preceded DM in 6 patients, and the 2 conditions were simultaneously diagnosed in 10 patients. Malignancy was found after the diagnosis of DM in only 1 patient. This contrasts somewhat with previous studies<sup>32,33</sup> reporting that the diagnosis of DM is made before the development of malignancy in at least half of patients. Regarding patients with anti-155/140 Abs, Chinoy et al<sup>34</sup> reported that malignancy preceded the onset of DM in only 1 of 8 patients. Two patients had DM and malignancies at the same time. The remaining 5 patients developed malignancies shortly after the diagnosis of DM. Although we currently cannot explain why the discrepancy that the diagnosis of malignancy preceded the onset of DM in a large portion of patients in our study, the discrepancy may have resulted from the timing of screening for malignancy because the interval between detection of the 2 conditions was short in most cases. Also, the discrepancy about the association of the diagnoses of malignancy with the onset of DM may be affected by center-based bias in collecting samples. Alternatively, ethnicity might account for the present data. More studies are required to confirm the relationship between the onset of DM and the development of malignancy.

Previous studies<sup>15,16,20</sup> have described at least 2 different subsets in patients with anti-155/140: adult malignancy-associated DM and juvenile DM. Although anti-155/140 was associated with malignancy, 32% of patients (8 of 25) did not have malignancy in this study. Although most patients with malignancy were elderly and male, clinical features were generally similar between patients with malignancy and those without except for punctate hemorrhages on the perionychium. In addition, clinical features in anti-155/140-positive adult patients without malignancy were similar to those seen in juvenile patients in that they had more extensive skin involvement, such as Gottron papules, over a wider distribution.<sup>16,20</sup> It is unclear why transcriptional intermediary factor 1- $\gamma$  is common as a major autoantigen in these 2 groups (adult malignancy and juvenile). Gunawardena

et al<sup>30</sup> proposed the possibility that some perturbation of transcriptional intermediary factor 1- $\gamma$  in proliferating cells combined with a more efficient anticancer response by a younger immune system may be important. Of interest is that patients with malignancy had a lower frequency of punctate hemorrhages on the perionychium compared with those without malignancy. Peripheral circulatory disturbances, including vasculopathy and microcirculation injury, are considered to be a hallmark of autoimmune connective tissue diseases. The lower frequency of punctate hemorrhages on the perionychium in patients with malignancy might be explained by the different mechanisms in developing skin and by muscle involvement between those with malignancy and those without, although both groups had the same Abs against transcriptional intermediary factor 1- $\gamma$ . Further investigation is needed to reveal the pathogenesis of these 2 subsets.

Interstitial lung disease is a crucial complication for patients with DM because the prognosis of ILD in DM varies. The severity, clinical course, and prognosis of ILD in DM vary, and ethnicity seems to affect the clinical presentation. In the United States, the frequency of ILD in patients with clinically amyopathic DM is low, and the prognosis is favorable if they do not have a malignancy.<sup>35-37</sup> On the other hand, patients developing RP-ILD have been frequently reported not only in Japanese individuals but also in Chinese individuals and those of other Asian ethnicity. For example, Lee et al<sup>38</sup> reported 2 cases of idiopathic inflammatory myopathy with diffuse alveolar damage. Ye et al<sup>39</sup> also reported that 21 of 28 patients with clinically amyopathic DM had ILD, and, even in classical DM, 50% of patients had ILD. The Asian population might be sensitive to lung damage accompanied by genetically susceptible factors because severe acute respiratory syndrome caused by a coronavirus prevailed predominantly in eastern Asia.<sup>40</sup>

It is considered that the Abs present are associated with a type of ILD. Interstitial lung disease in anti-ARS-positive patients is characterized by the chronic course of the disease and elevation of the diaphragm.<sup>41</sup> Detection of anti-CADM-140 is extremely important because patients with anti-CADM-140 can frequently develop RP-ILD. Therefore, predictors of poor prognosis in this subgroup are needed. Skin ulcers, arthralgia or arthritis, lower arterial PO<sub>2</sub>, and higher lactate dehydrogenase levels are considered to be risk factors for poor prognosis.<sup>39</sup> It is also reported that anti-CADM-140-positive patients with RP-ILD have rashes typically seen in DM.<sup>24</sup> In other studies,<sup>42,43</sup> spontaneous pneumomediastinum or pneumothorax is a severe complication and may indicate poor prognosis. However, the clinical phenotype was otherwise similar between patients with a poor prognosis and those with a favorable prognosis in this study.

To establish the treatment for RP-ILD is another urgent issue that needs a solution. Cyclophosphamide and cyclosporine are recommended in the early phase of the disease.<sup>41,44</sup> In contrast, Lee et al<sup>38</sup> reported that 4 patients with RP-ILD received 1 course of intravenous cyclophosphamide therapy and additional cytotoxic agents, such as azathioprine, cyclosporine, and methotrexate, but none responded. In this study, we could not elucidate definite predictors of poor prognosis and recommended

treatment. Thus, it might be required to attempt the maximum possible combination of immunosuppressive treatments when patients with anti-CADM-140 present signs of developing RP-ILD.

In conclusion, classifying patients with DM according to their DM-specific Abs may guide the physician to focus on particular manifestations with high risk during follow-up of individual patients. However, the detection of DM-specific Abs is limited only to certain facilities because it requires a complicated technique. Establishment of a system to screen DM-specific Abs, such as an enzyme-linked immunosorbent assay, is needed. We acknowledge several limitations of this study. First, it included a relatively small number of patients with PM as a control because most enrolling institutions were dermatology departments. Second, we did not include juvenile patients with DM and other juvenile patients with connective tissue diseases. Third, anti-NXP-2 Abs were not included in this study because they are extremely rare in Japanese patients with DM. In addition, most of the facilities enrolled in this study were referral centers. Therefore, the possibility of center-based bias in collecting samples cannot be ruled out. More studies are needed for a better general understanding of patients with DM-specific Abs.

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